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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,992	LONGENECKER, B. MICHAEL	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-11,13-18,20-29 and 31-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-7, 9-11, 13-18, 20-29 and 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed on 12/17/2009 in response to the Non-Final office action of 6/17/2009 is acknowledged and has been entered.

Claims 1, 3-7, 9-11, 13-18, 20-29 and 31-40 are currently pending and under consideration.

Rejections Maintained, but Amended in view of Applicants Amendments:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-5, 7-11, 13-18, 20-21, 23, 24, 25-29 and 31-32 remain rejected and new claims 33-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al .(Clinical Lung Cancer 2001; 3 (1): 49-57) in view of Sugiura et al. (Clinical Cancer Research 1999; Vol. 3: 47-50).

Palmer et al. teach a method of treating an individual with non-small cell lung cancer stage IIIB or IV comprising: (a) selecting for treatment an individual who has small cell lung cancer stage IIIb or IV; (b) administering a priming dose of cyclophosphamide; and (c) administering to that individual an amount of a formulation comprising a liposome comprising a 20 or 200 μg of a MUC-

1 lipopolypeptide referred to as BLP25, 100 mg of Lipid A and 20 mg/mL liposomal lipids (dipalmitoyl phosphatidhylcholine, cholesterol and phosphatidylglyceral) (see page 51, Treatment Plan, Page 50, Vaccine Preparation and Patient Selection). With regards to the administration, Palmer et al. teach that the formulation was administered via subcutaneous injection at weeks 0, 2, 5 and 9, as well as at 3 month intervals (page 51, 2nd column, Treatment Plan). With regards to BLP25, the reference teaches that the palmitoyl lysine residues at the carboxy terminal was included in BLP25 to enhance the incorporation of BLP25 into the liposome particle (page 50, Vaccine Preparation). Palmer further teaches that the patients were evaluated prior to treatment to serve as a base line, during each vaccination treatment and at week 11 and 15. In particular, the reference teaches that patients were evaluated for tumor response, immune response, T-cell proliferation, survival rate of the individual and changes in the individual's quality of life (page 51, Patient Evaluation, Immunological Assays and page 53, Outcome Evaluation and paragraph bridging page 55 and 56). Lastly, the reference teaches that, as a group, patients with advanced stage NSCLC have a much shorter natural history and overall survival than patients with breast and some other cancers, which may be important considerations in explaining why some of these patients failed to demonstrate an immune response on this prolonged vaccination (page 55, 2nd column, last paragraph).

Note: BLP25 is a 25 mer comprising the amino acid sequence of STAPPAHGVTSAPDTRPAPGSTAPP, e.g., SEQ ID NO: 1, further containing Two non-muc-1 amino acids added as a scaffold for attaching the lipid tail, making it a total of 27 amino acids comprises the following amino acid sequence STAPPAHGVTSAPDTRPAPGSTAPPKG, e.g., SEQ ID NO: 2 or a variant of SEQ ID NO: 1. BLP25 has a palmitoyl group at the epsilon amino group of the C-terminal lysine giving the molecule the following structure STAPPAHGVTSAPDTRPAPGSTAPP(K-palmitoyl)G, e.g., a variant of SEQ ID NO: 2, see WO 02/43699, page 9, lines 7-12.

Furthermore, the "wherein clause" as recited in amended claim 18 and new claims 39-40 have not been given any patent weight since it simply expresses the intended result of the process of step of "administration" positively recited.

Palmer et al. does not specifically teach selecting patients having stage IIIB locoregional (without malignant pleural effusion) NSCLC and administering said formulation to said patient.

Sugiura et al. disclose assessing the survival times of patients with stage IIIB without effusion, stage IIIB with effusion and stage IV NSCLC. In particular, the reference teaches that survival times of stage IIIB with effusion was significantly different from that of stage IIIB without effusion, but not from that of stage IV, e.g., 15.3 months for stage IIIB without pleural effusion, 7.5 months for stage IIIB with pleural effusion and 5.5 months for stage IV (page 48, paragraph bridging 1st and 2nd column (abstract). In view of this, the reference teaches that stage IIIB patients with pleural effusion should be regarded as a separate prognostic group than stage IIIB without pleuroal effusion (page 49, 2nd column). Therefore, the reference teaches that distinguishing between stage IIIB with pleural effusion from stage IIIB without pleural effusion is necessary for treatment selection, since patients with pleural effusion cannot be treated with combined chemotherapy and radiotherapy which are accepted as standard treatment for locally advanced NSCLC (page 50, 1st column, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to modify the method taught by Palmer et al .to select patients suffering from stage IIIB locoregional (without malignant pleural effusion) in view of the teachings of Sugiura et al. One would have been motivated to do so because as taught by Sugiura et al., stage IIIB patients with pleural effusion should be regarded as a separate prognostic group than stage IIIB without pleuroal effusion and further, survival times of stage IIIB with effusion are significantly different from that of stage IIIB without effusion, but not from that of stage IV, e.g., 15.3 months for stage IIIB without pleural effusion, 7.5 months for stage IIIB with pleural effusion and 5.5 months for stage IV. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Palmer et al .to select patients suffering from stage IIIB locoregional (without malignant pleural effusion) in view of the teachings of Sugiura et al., one would achieve a longer survival time to induce an immune response to the prolonged vaccination with BLP25.

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments as they relate to the present rejection. In response to the previous rejection, Applicants assert that a person of ordinary skill in the art would appreciate that this was a mere "phase I safety profile and dose comparison study", designed to determine the “safety profile” of the BLP25 liposomal vaccine and “its ability to generate an anti-MUC1 immune response.” (page 50, top of

column 2). However, Applicants note that eliciting an immune response doesn't imply that the drug provides a clinically meaningful improvement in survival. Moreover, Applicants contend that while the Palmer patients were identified as having either IIIB or IV stage non-small cell lung cancer, there is no breakdown, of median survival between Stage IIIB and stage IV, let alone between IIB with and IIIB without pleural effusion. Thus, Applicants asset that this implies that the Palmer group did not believe that the distinction was a clinically relevant one. Applicants further point out that in the later phase II study (Butts 2005, copy enclosed), it was expected that only 10% of the enrolled patients would have stage IIIB LR and 90% would have IIIB-MPE or IV. With regards to Sugiura, Applicants contend that Sugiura identified pleural effusion as a "significant prognostic factor". For example, Applicants contend that looking at Figure 1 of Sugiura, we estimate two year survival as being approximately 17% for IIIB with pleural effusion, approximately 43% for IIB without and approximately 7% for IV. Moreover, Applicants contend that as noted by Sugiura, patients with IIIB locoregional disease can be treated with combined chemotherapy and radiotherapy, whereas those with IIIB with malignant pleural effusion cannot (page 50, col. 1). Hence, Applicants assert that even if Palmer's data were sufficient to persuade the art that BLP25 liposomal vaccine was efficacious against NSCLC, Sugiura would motivate the skilled worker to use it to treat the conditions not susceptible to chemotherapy, e.g, IIIB-MPE and IV. Applicants further contend that if Palmer is evidence of a protecting effect at all, it is on stage IV patients. For example, Applicants contend that from the Kaplan-Meier survival curve, it can be seen that eight patients in the 200 group had the following survivals (estimated from the figure): 3,4,8,14,15,16,18.5 and 27. Thus, if we assume that there were two IIIB patients in the survival analysis, and that they were the two longest survivors, we would be left with a median stage IV survival of 11 (average 8 and 14) which is twice the 5.5 reported by Sugiura. Additionally, Applicants contend that if there were three IIIB patients, and they were the three longest survivors, the median stage IV survival would be 8. Thus, Applicants contend that since the putative effect was manifested after a nine week immunization, there is insufficient reason to infer that the longer "grace period" offered by Sugiura's stage IIIB LR patients would be needed in order to achieve an increase in survival. Furthermore, Applicants respectfully assert that the present specification evidences an unexpectedly superior result, i.e., we helped patients with IIIB locoregional more than could be expected given their normal survival rates, given the improvement that would reasonably be expected from Palmer to be attributable to

BLP25 treatment. For example, Applicants direct the Examiner's attention to the survival study reported in the patent application (see pages 35-37 and Figures 1 and 2). In particular, Applicants direct the Examiner's attention to Figure 2 and the hazard ratio, wherein the hazard ratio extends only slightly about 1, but down as low as 0.2607 (i.e., risk reduction of 74%) which are extremely promising results. Moreover, Applicants also contend that the differences in two year survival, as well as the quality of life comparisons are also quite promising and are not addressed in either Palmer and/or Sugiura. Applicants further contend that post-filing results provided by Sangha and Butts, Clin. Cancer Res. 2007; 13: 1452s-4654s and Butts et al., J. Clin. Oncol. 2005; 23: 6674-6681 show extended survival data and confirm that the drug may be of substantial clinical importance. In particular, Applicants assert that our phase 2b trial, which is what the patent application is based on, showed a 17.3 months survival benefit in the stage III-LR population which is entirely unexpected in light of the Palmer 2001 data which showed around 9 month survival benefit. Moreover, Applicants contend that using our Figure 1 overall survival data as a surrogate for Palmer's overall survival from 13 months to 17.4 months, which is an absolute change of 4.4 months, but about a one-third improvement. In contrast, Applicants contend that our Figure 2, relating to just the IIIB-LR subpopulation, shows an improvement in median survival from 13.3 (Control) to a minimum of 24 months, thus an increase of 10.7 months, or nearly 100%. Thus, Applicants contend that one relying on Figure 1 as evidence of the quantitative effect of BLP25 arguably would expect it to provide a one third improvement, e.g., to a bit over 20 months using the 15.3 month medium survival observed by Sugiura. Therefore, the median survival follow up shown by the 2007 post filing paper of almost 31 months is an unexpected superiority.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants arguments with regards to Palmer, the Examiner acknowledges and does not dispute Applicants contention that Palmer is directed to phase I safety and dose comparison study designed to determine the “safety profile" of the BLP25 liposomal vaccine. However, the Examiner recognizes that Palmer et al. clearly teaches at least one of the active steps involved in the instant claims, e.g., administration of 200 μg of a liposomal formulation comprising BLP25, wherein the specification teaches that about 200 μg is a suitable dosage of BLP25 (see specifciation page 15, lines 4-20). Moreover, the Examiner recognizes that Palmer clearly teaches an improvement in survivability, e.g., 20 μg compared to the 200 μg. Thus, while Palmer does not

explicitly teach that this is "clinically meaningful", the Examiner has carefully reviewed the instant specification and can not find any definition of what a "clinically meaningful improvement in survival" encompasses. It would appear that an increase from 5.4 months in the 20 μg group to 14.6 months in the 200 μg group would be a clinically meaningful improvement in survivor ability. Moreover, with regards to Applicants arguments pertaining to Palmer not teachings a distinction between Stage IIIB, Stage IV and/or Stage IIIB with/without, the Examiner acknowledges and does not dispute these facts. However, the Examiner acknowledged this distinction and used Sugiura in combination with Palmer to meet these limitations. Regarding Applicants opinions with regards to why Palmer did not do this, the Examiner recognizes that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). In the present case, a careful review of Palmer does not appear to imply that Palmer did not believe this distinction to be clinically relevant. As such, it is unclear of how Applicants came to this conclusion. Similarly, Applicants conclusionary statement with regards to Sugiura would motivate the skilled worker to use BLP25 to treat the conditions not susceptible to chemotherapy appears to be an opinion which is not supported by any factual evidence as to why one would only treat these patients. Accordingly, such arguments have not been considered. With regards to Applicants data extrapolation of Palmer to evidence a protecting effect to only stage IV patient, the Examiner acknowledges and appreciates Applicants analysis. However, the Examiner recognizes that this type of analysis is up to one's own interpretation. For example, if we were to assume that three of the IIB patients had the following survivals 8, 15, 18.5, the medium survival would be 15 for IIIB and 14 for the Stage IV. This would equate to an approximate 2.5 time increase in the survival rate for both the stage IIIB and IV patients since the median survival times of 14 and 15, e.g., IIB and IV respectively, appear to be not statistically significant and appears to be show a protective effect for both the IIIB and IV patients. With regards to Applicants arguments pertaining to the unexpected superior results, the Examiner acknowledges and has carefully reviewed the specification, as well, as the post filing references. However, the Examiner notes the following: First, the experiments performed in the present specification and post filing references do not appear to be commensurate in scope with the claimed invention. In particular, the liposomal formulation is defined in the specification as consisting of 1000 ug of BLP25 lipopeptide, 500 mg immunoadjuvant monosphosphoryl lipid A and three lipids (i) 17.3 mg cholesterol, (ii) 3.6 mg dimyristoyl

phosphatidylglycerol and (iii) 29.1 mg dipalmityoyl phosphatidylcholine. However, the present claims do not claim an embodiment with all of these defined components. Moreover, the Experiments (see example 1 of the instant specification) at least within the specification were run in combination with BCS and it is unclear what effect BCS in combination with BLP25 had on the median survival. In contrast, BSC was not carried out in the Palmer reference. Accordingly, a direct comparison can not be made. Additionally, there appears to be a reasonable expectation that administration of more of BLP25, e.g., 200 μg vs 1000 μg, would increase the survivability since Palmer clearly teaches an improvement in survivability the 20 μg compared to the 200 μg. Secondly, the Examiner acknowledges and does not dispute Applicants contention that the results of Figure 2 and the hazard ratio represents extremely promising results. However, the Examiner recognizes that it is unclear how these results represent unexpected results. Thirdly, the Examiner acknowledges and has carefully reviewed the post filing evidence. Yet, similar to the response set forth above, the post filing evidence does not appear to commensurate in scope with the claimed invention. Additionally, it is important to note that Applicants appear to refer to the phase IIB study taught by post filing reference Butts et al. as "our phase 2b trial", which is what the patent application is based on. Yet, a careful review of the reference does not appear to have an inventor in common. As such, the record is beginning to get unclear as to who invented the current invention. Lastly, regarding Applicants arguments pertaining to Figure 1 as a surrogate for Palmer's overall survival data as compared to Figure 2, relating to just the IIIB-LR subpopulation, the Examiner acknowledges and has carefully reviewed both Figures 1 and 2, as well as Example 1 of the specification. However, the Examiner recognizes the following inconsistencies with Applicants conclusions. First, it is important to note that the Example 1 of the specification describes the controlled, open-label Phase IIb trial which enrolled 171 patients, wherein 65 had IIIB locoregional disease. Of these, 35 were randomized to treatment and 30 were randomized to best standard care (BSC) (best standard care includes pallative radiotherapy and/or second line chemotherapy according to current standard clinical practice (see specification page 38, lines 6-7)). Thus, while the specification does not explicitly state this, it can be assumed that the treatment arm for the results of Figure 1 overall survival encompassed 88 patients (53 with Stage IIIB with/stage IV and 35 with Stage IIIB without) and the BSC encompass 83 patient (53 with Stage IIIB with/Stage IV and 30 with Stage IIIB without). With regards to Figure 2, it can be assumed that the figure depicts the

results of 35 patients with Stage IIIB without randomized to treatment compared to the 30 randomized to best standard care. Thus, it is not surprising that that the medium survival of Figure 1 as compared to Figure 2 is dramatically different since there is a large population, e.g., 62.5 %, of patients with Stage IIIB/IV which have a lower median survival as taught by Sugiura. In other words, there would be a reasonable expectation that just the IIIB-LR subpopulation would have a longer median survival since the study would exclude the lower median survival populations which would lower the median survival. Additionally, as set forth above, the trials were also done in combination with BSCand as implied by Sugiura, Stage IIIB without is treatable with BSC. Accordingly, it is unclear what effect the combination of BSC and BLP25 had on the median survival of the selected population. Thus, it appear that Applicants reliance on Figure 1 in view of what was observed by Sugiura for locoregional IIIB patients for the extrapolation of a one third improvement for the IIIB locoregional patients is misleading since the median survival takes into account the patients having Stage IIIB with/IV patient population which are known to have shorter median survivals.

Claim 22 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al .(Clinical Lung Cancer 2001; 3 (1): 49-57) in view of Sugiura et al. (Clinical Cancer Research 1999; Vol. 3: 47-50), as applied to claims 1, 3-5, 7-11, 13-18, 20-21, 23, 24, 25-29 and 31-40 above, in further view of Palmer et al. (Annals of Oncology 2000; 11 (supplement 4): page 42, Abstract 179PD, referred to herein as Palmer 2).

Palmer et al. teach a method of treating an individual with non-small cell lung cancer stage IIIB or IV comprising: (a) selecting for treatment an individual who has small cell lung cancer stage IIIb locoregional (without pleural effusion); (b) administering a priming dose of cyclophosphamide; and (c) administering to that individual an amount of a formulation comprising a liposome comprising a 20 or 200 μg of a MUC-1 lipopolypeptide referred to as BLP25 (Same as SEQ ID NO: 1, see applicants remarks to the Restriction Requirement), 100 mg of Lipid A and 20 mg/mL liposomal lipids (dipalmitoyl phosphatidhylcholine, cholesterol and phosphatidylglyceral) (see page 51, Treatment Plan, Page 50, Vaccine Preparation and Patient Selection).

Palmer et al. in view of Sugiura et al. do not explicitly teach that BLP25 was administered at a dose of 1000 μg and Lipid A is at a dose of 500 μg.

Palmer 2 teaches a phase I/II trial of BLP25 administered at a dose of 1000 μg subcutaneously weekly for 8 weeks in patients with metastatic stage IIIB and IV non-small cell carcinoma of the lung. In particular, the abstract teaches that BLP25 in a dose of 1000 μg s/c is well tolerated and produces a dose dependent anti-MUC1 specific cellular immune response in NSCLC.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to optimize the amount of BLP25 and Lipid A in the formulation taught by Palmer et al. in view of the teachings of Palmer 2. One would have been motivated to do so because Palmer 2 teaches that BLP25 in a dose of 1000 μg s/c is well tolerated and produces a dose dependent anti-MUC1 specific cellular immune response in NSCLC. With regards to the amount of Lipid A, the court has found that"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). As such, one of ordinary skill in the art would have a reasonable expectation of success that by optimizing the amount of BLP25 and Lipid A in the formulation taught by Palmer et al. in view of the teachings of Palmer 2., one would achieve a method of inducing an immune response.

In response to this rejection, Applicants contend that the abstract provides only limited information on treatment results and provide not info on how many patients out of the eight have IIIB or IV. Thus, Applicants contend that the abstract teaches the claimed BLP25, it doesn't overcome the deficiencies already noted above.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above and incorporated herein.

Claim 6 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al .(Clinical Lung Cancer 2001; 3 (1): 49-57) in view of Sugiura et al. (Clinical Cancer Research 1999; Vol. 3: 47-50), as applied to claims 1, 3-5, 7-11, 13-18, 20-21, 23, 24, 25-29 and 31-40 above, in further view of Morse et al. (Current Opinion in Molecular Therapeutics 2001; 3: 102-105).

Palmer et al. teach a method of treating an individual with non-small cell lung cancer stage IIIB or IV comprising: (a) selecting for treatment an individual who has small cell lung cancer stage IIIb locoregional (without pleural effusion); (b) administering a priming dose of cyclophosphamide; and (c) administering to that individual an amount of a formulation comprising a liposome comprising a 20 or 200 μg of a MUC-1 lipopolypeptide referred to as BLP25 (Same as SEQ ID NO: 1, see applicants remarks to the Restriction Requirement), 100 mg of Lipid A and 20 mg/mL liposomal lipids (dipalmitoyl phosphatidhylcholine, cholesterol and phosphatidylglyceral) (see page 51, Treatment Plan, Page 50, Vaccine Preparation and Patient Selection).

Palmer et al. in view of Sugiura et al. do not explicitly teach that the formulation comprises IL-2.

Morse et al .teach that the use of BLP-25 has been initiated in a phase IIb trial in advanced NSCLC to determine if higher or more frequent dosing would enhance its effects (page 103, 1st column, Phase II). Morse et al .further teach that the next phase of development is to administer BLP-25 in combination with liposomal IL-2, wherein the purpose of the study is to determine if the effect of BLP-25 is enhanced by IL-2 (page 103, 1st column, Phase II).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to modify the method taught by Palmer et al. to further include IL-2 in view of the teachings of Morse et al. to determine if the effect of BLP-25 is enhanced by IL-2. Thus, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, one of skill in the art would have a reasonable expectation of success that by modifying the method taught by Palmer et al. to further include IL-2 in view of the teachings of Morse et al., one would achieve a method of enhancing the immune response of BLP-25.

No arguments have been presented by Applicants with respect to this rejection. Accordingly, the rejection is maintained.

Therefore, No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642